

## Transient Apical Ballooning

# Four-Year Recurrence Rate and Prognosis of the Apical Ballooning Syndrome

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<b>Objectives</b>	This study sought to assess the long-term prognosis of patients with apical ballooning syndrome (ABS).
<b>Background</b>	Apical ballooning syndrome is a recently described acute cardiac syndrome of uncertain etiology and prognosis.
<b>Methods</b>	We retrospectively identified 100 unselected patients with a confirmed diagnosis of ABS by angiography. Recurrences of ABS and mortality were recorded.
<b>Results</b>	Over a mean follow-up of $4.4 \pm 4.6$ years, 31 patients continued to have episodes of chest pain and 10 patients had recurrence of ABS, for a recurrence rate of 11.4% over the first 4 years. Seventeen patients died in $4.7 \pm 4.8$ years of follow-up. There was no difference in survival or in cardiovascular survival to an age- and gender-matched population.
<b>Conclusions</b>	The recurrence rate for ABS was 11.4% over 4 years after initial presentation. Recurrence of chest pain is common. Four-year survival was not different from that in an age-matched and gender-matched population. (J Am Coll Cardiol 2007;50:448–52) © 2007 by the American College of Cardiology Foundation

Apical ballooning syndrome (ABS) is a recently described acute cardiac syndrome (1). Several series have described the clinical features of the syndrome (2–8). Some reports have described recurrence of ABS (3–6), and a few reports have described the short-term prognosis (5,6). However, most of these series were small cohort studies (2–4,6,7) and none reported the recurrence rate and the long-term prognosis of ABS.

The goal of the current study was to assess the recurrence rate of ABS after initial presentation and the factors associated with ABS recurrence, and the long-term survival of patients with ABS and identification of factors that influence survival with ABS.

## Methods

**Patients.** This study was approved by the Mayo Foundation Institutional Review Board. We searched the Mayo Cardiac Catheterization Laboratory database from January 1988 through November 2005 for patients who underwent both coronary and left ventricular angiography and met the previously described Mayo Clinic criteria for ABS (1). Our initial search was restricted to patients with coronary artery

diameter stenoses <30% and apical hypokinesis, akinesis, or dyskinesis with sparing of the basal segments. This search yielded 545 potential patients; 421 were excluded for other cardiac diagnoses. Of the remaining 124 patients, 102 met the criteria for the clinical identification of ABS (1). Two of these could not be contacted on follow-up. Thus, 100 patients comprised the study population.

The complete medical record and angiographic studies of each patient were reviewed. An ST-segment elevation was defined as deviation >1 mm in amplitude in more than 2 contiguous leads, and deep T-wave inversion was defined as inversions >3 mm in amplitude in at least 3 contiguous leads. All other electrocardiographic (ECG) changes that did not fulfill these criteria were grouped under nonspecific ST/T-wave changes.

A measurement of left ventricular ejection fraction by echocardiography was done according to the Simpson rule (9). Angiography was performed at presentation in 81 patients, on the second day in 12 patients, on the third day in 5 patients, and on the fourth day in 2 patients. A measurement of left ventricular ejection fraction by biplane contrast left ventriculography was carried out by the mono-plane area-length method (10).

**Clinical follow-up.** Follow-up data were collected through detailed review of all medical records. Mailed questionnaires and telephone interviews with patients also were used to complete follow-up. For a diagnosis of recurrence, the

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proposed Mayo criteria for the clinical diagnosis of ABS had to be met with repeat coronary angiography (1). The cause of death was confirmed by review of all available clinical information at the time of death and by review of death certificates.

**Statistical analysis.** Continuous data are summarized as mean  $\pm$  SD unless otherwise noted. Frequencies and percentages are used to describe discrete variables. Kaplan-Meier methods were used to estimate long-term survival. A

Poisson model was used to estimate 95% confidence intervals for event rates per person-year. The incidence of recurrence of ABS over time was estimated in a competing risks scenario, with death as the competing event (11). Simple hazard ratios for follow-up mortality were computed using Cox proportional hazards models.

The risk of mortality (total and cardiac) observed in our study cohort was compared with modeling of the expected risk of mortality using data derived by applying age-, gender-, and birth-year-specific mortality rates from the Minnesota white population (12,13) to the age-, gender-, and birth-year-specific person-years of follow-up in this cohort. Population rates were not available after the year 2002, so 2002 rates were carried forward for subsequent years. One-sample log-rank tests were used to compare the observed and expected cardiac event rates (14).

#### Abbreviations and Acronyms

**ABS** = apical ballooning syndrome  
**ECG** = electrocardiographic/electrocardiography

**Table 1** Patient Clinical Characteristics

	Total Population
n	100
Age $\pm$ SD, yrs	66 $\pm$ 13
Female (%)	95 (95%)
Hypertension (%)	52 (52%)
Diabetes mellitus (%)	5 (5%)
Hyperlipidemia (%)	33 (33%)
Tobacco use	
Never (%)	62 (62%)
Past (%)	20 (20%)
Current (%)	18 (18%)
Presentation	
Chest pain (%)	77 (77%)
Dyspnea (%)	8 (8%)
Other (%)	15 (15%)
Days of hospitalization, median (25th, 75th interquartile)	5 (4, 8)
Congestive heart failure at presentation (%)	44 (44%)
Intubation (%)	10 (10%)
IABP insertion	7 (7%)
Electrocardiography	
ST-segment elevation* (%)	33 (33%)
Deep T-wave inversion† (%)	31 (31%)
Nonspecific ST-T-wave $\Delta$ (%)	33 (32%)
Left bundle branch block (%)	3 (3%)
Atrial fibrillation (%)	6 (6%)
Maximal QTc‡ $\pm$ SD, ms	513 $\pm$ 65
Cardiac angiogram	
Ejection fraction $\pm$ SD, %	46 $\pm$ 14
LVEDP $\pm$ SD, mm Hg	23 $\pm$ 8
Initial ejection fraction $\pm$ SD, % (by echocardiography) (n = 57)	40 $\pm$ 13
Follow-up ejection fraction $\pm$ SD, % (by echocardiography)	61 $\pm$ 7
Maximal creatinine $\pm$ SD, mg/dl	1.1 $\pm$ 0.4
Troponin T, ng/ml, median (25th, 75th interquartile) (n = 47)	0.5 (0.2, 1.0)
Discharge medication	
Beta-blockers (%)	56 (56%)
ACEI/ARB (%)	51 (51%)
Aspirin (%)	74 (74%)
Statins (%)	32 (32%)

Unless otherwise specified, the data were available on all patients. \*ST-segment elevation had an anterior or anterolateral distribution in 26 of the 33 patients with ST-segment elevation (79%), was diffuse in 5 cases (15%), and was inferior or lateral in 2 cases (6%). †With anterior or anterolateral distribution in 16 of the cases, diffuse in 10 cases, and inferior or lateral in 5 cases. ‡71 patients had a prolonged corrected QT interval on electrocardiogram ( $>460$  ms).

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; IABP = intra-aortic balloon pump insertion; LVEDP = left ventricular end-diastolic pressure; QTc = corrected QT interval.

## Results

**Clinical characteristics.** Clinical characteristics for the entire cohort are summarized in Table 1. All 100 study patients were white. Most patients were local residents, with 66 patients living within a 60-mile radius of the hospital, and 92 within a 120-mile radius. Troponin T levels were available for 47 patients and showed elevation in all but 1 patient. A summary of identifiable precipitating events for the ABS is provided in Table 2.

**Presentation and hospital outcome.** The most common presentation of patients with ABS was the combination of chest pain, ECG abnormalities, and a mild elevation in cardiac biomarkers.

The left ventricular ejection fraction was depressed at presentation in all patients, with normalization at a median of 69 days from presentation (interquartile range 27 to 348 days). Coronary angiography at initial evaluation indicated a normal left anterior descending artery in 41 patients and mild stenoses ( $<30\%$ ) in 59 patients.

During the index hospitalization, 6 patients had life-threatening arrhythmias: 1 patient presented with a ventricular fibrillation arrest; 1 patient presented with ventricular tachycardia and cardiac arrest; 2 patients presented with second-degree atrioventricular block, 1 of whom subsequently required permanent pacemaker implantation; and 2 patients had asystolic arrest during hospitalization. Two patients died during index hospitalization, both after a cardiac arrest, 1 with ventricular fibrillation and 1 with asystole.

Discharge medications are listed in Table 1. When the population was stratified according to year of presentation (1988 to 1993 vs. 1994 to 1999 vs. 2000 to 2005), use of beta-blockers (17% vs. 44% vs. 74%,  $p < 0.001$ ), angiotensin-converting enzyme inhibitors/angiotensin re-

Table 2    Precipitating Factors	
Identifiable Precipitating Factors	
Emotional stressor	26
Death of a family member	8
Severe argument	5
New diagnosis of personal disease	4
Involvement in a minor car accident	3
Public speech	2
Daughter's divorce	1
Dog caught in a raccoon trap	1
New diagnosis of a disease in a family member	1
Move to a new residence	1
Casino loss	1, at recurrence
Physical stressor	30
Noncardiac surgery or procedure	12
Severe illness	5
Fracture	4
Asthma/COPD exacerbation	4
Stroke/transient ischemic attack	2
Pneumothorax	1
Pulmonary embolism	1
Renal colic	1
No identifiable stressor	44

COPD = chronic obstructive pulmonary disease.

ceptor blockers (17% vs. 36% vs. 64%,  $p < 0.001$ ), and statins (6% vs. 28% vs. 42%,  $p = 0.01$ ) increased significantly, whereas the use of aspirin did not change (83% vs. 64% vs. 75%,  $p = 0.34$ ).

**Events occurring during follow-up.** Follow-up information was available for all 100 patients. Most patients were local residents and subsequently returned to Mayo Clinic for their general medical care. The frequency of returns was variable. Data from multiple return visits were available for 84 patients. The other 16 patients were sent questionnaires and contacted by telephone if no response was received.

**Recurrence of ABS.** The ABS recurred in 10 patients over a mean follow-up of  $4.4 \pm 4.6$  years. Figure 1 shows the Kaplan-Meier estimated rate of ABS recurrence. The recurrence rate was highest within the first 4 years at about 2.9% per year, subsequently decreasing to about 1.3% per year over the remainder of follow-up. The relatively small number of patients and recurrences did not allow meaningful statistical analysis of factors predicting the recurrence of ABS.

Of note, only 2 patients had an identifiable precipitating event at recurrence (pneumothorax in 1 and significant money loss at the casino in another). The ejection fraction was  $38 \pm 16\%$ . One patient died at recurrence secondary to ventricular fibrillation arrest.

Medical therapy at the time of last follow-up was not different from that started at the index evaluation for any treatment studied (data not shown). At the time of recurrence of ABS, there was no difference between the patients who did and did not have recurrence in the use of aspirin (60% vs. 67%,  $p = 0.67$ ), angiotensin-converting enzyme

inhibitors/angiotensin receptor blockers (60% vs. 51%,  $p = 0.59$ ), beta-blockers (80% vs. 52%,  $p = 0.10$ ), and statins (40% vs. 33%,  $p = 0.67$ ).

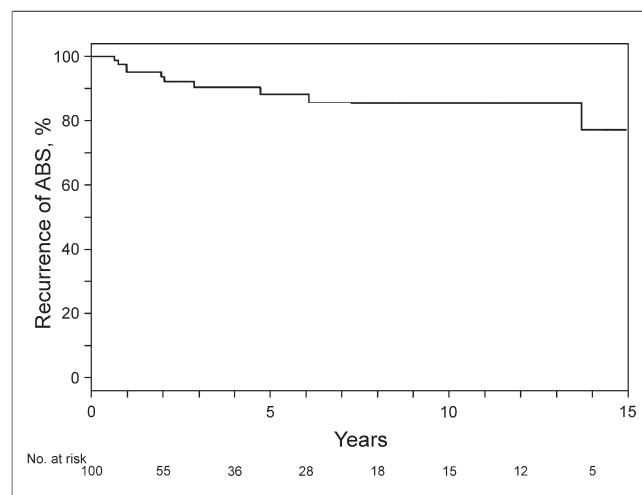
**Morbidity.** A total of 31 patients continued to experience episodes of chest pain. Of these 31 patients, 12 had chest pain resulting in at least 1 hospital admission, with 3 having repeat coronary angiography showing nonobstructive coronary atherosclerosis. Two patients had progression to severe congestive heart failure requiring in-patient treatment (in 1 case, repeat echocardiography showed normal ejection fraction). Only 1 patient (male) had progression of coronary atherosclerosis requiring bypass surgery more than 16 years after the index presentation.

**Mortality.** Seventeen patients died over a mean follow-up of  $4.7 \pm 4.8$  years. Table 3 summarizes the causes of death. Table 4 summarizes univariate models for predictors of death after ABS index presentation. Multivariate analysis was not possible because of the small number of events.

Figure 2 shows the survival estimates of the population, as well as the expected survival for an age-, gender-, birth year-, and race-matched population. Mortality did not differ significantly between our study population and the matched control population. Figure 3 shows the cardiovascular survival estimates of the population, as well as the expected cardiovascular survival for an age-, gender-, birth year-, and race-matched population. Cardiovascular mortality did not differ significantly between our study population and the matched control population.

## Discussion

This series of 100 patients with ABS clarifies important issues related to the natural history of ABS. First, recurrence of ABS is infrequent. Second, 4-year survival of patients



**Figure 1**    Recurrent Rate of ABS

Kaplan-Meier curve showing recurrence of apical ballooning syndrome (ABS) over time for the total patient population. Number of patients still at risk is noted at 2-year intervals below the time axis.

**Table 3** Causes of Death

Causes of Death	
Arrhythmia	5
Aortic stenosis*	1
Lower-extremity arterial embolism	1
Malignancy	7
Lung cancer	1
Colon cancer	1
Leukemia	1
Bladder cancer	1
Breast cancer	2
Lymphoma	1
COPD	3
AML	1

\*Death from aortic stenosis occurred 16 years after index presentation with apical ballooning syndrome, at which time no significant aortic stenosis was detected.

AML = amyotrophic lateral sclerosis; COPD = chronic obstructive pulmonary disease.

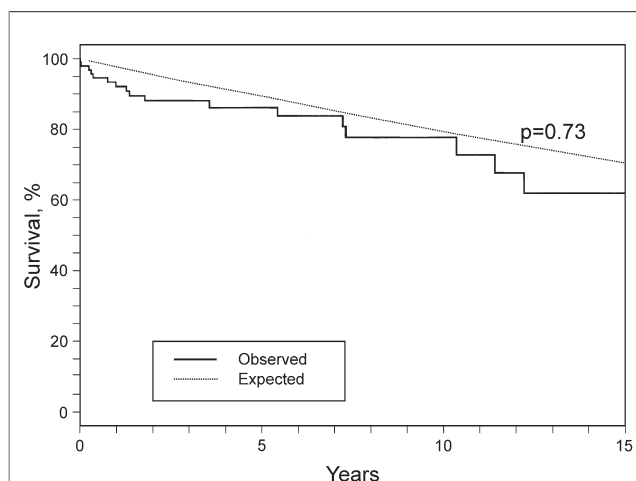
with ABS is similar to the expected survival for an age-, gender-, birth year-, and race-matched population.

Patients with ABS have a presentation similar to that for an acute coronary syndrome. Despite the considerable morbidity with which these patients present, most patients survive the index hospitalization with adequate medical support. In the present report, in-hospital mortality was low (2%) and generally caused by a cardiac arrhythmia. These findings compare favorably with the reported rates of in-hospital mortality of 9% to 10% in nonselected case series of myocardial infarction (15,16).

**Table 4** Univariate Analysis for Predictors of Death After ABS Index Presentation

Variable	Hazard Ratio	Lower Value	Upper Value	p Value
Male	0.91	0.12	6.91	0.93
Age (per decade)	1.49	0.97	2.29	0.069
Hypertension	0.53	0.20	1.43	0.21
Hyperlipidemia	0.85	0.30	2.42	0.76
Ever smoked	0.90	0.33	2.44	0.83
Initial ejection fraction at angiography (per 10%)	0.64	0.44	0.94	0.023
LVEDP (per 10 mm Hg)	1.02	0.57	1.82	0.96
Congestive heart failure	1.36	0.53	3.55	0.52
Intubation	10.1	2.77	36.7	<0.001
Log2 troponin	1.18	0.66	2.10	0.58
Log2 creatinine	1.67	0.57	4.91	0.35
Electrocardiography results*				0.44
Nonspecific ST/T segment	1.00	—	—	
ST-segment elevation	2.12	0.67	6.75	0.20
Deep T-wave inversion	1.47	0.42	5.14	0.55
Maximal QTc (per 50 ms)	1.18	0.79	1.79	0.41
Beta-blockers at discharge	0.80	0.28	2.29	0.68
ACEI/ARB at discharge	1.28	0.46	3.52	0.64
Aspirin at discharge	0.68	0.24	1.96	0.47
Statins at discharge	0.43	0.10	1.95	0.27

\*Excluding the 3 patients with left bundle branch block, in whom there were no follow-up deaths.  
ABS = apical ballooning syndrome; other abbreviations as in Table 1.

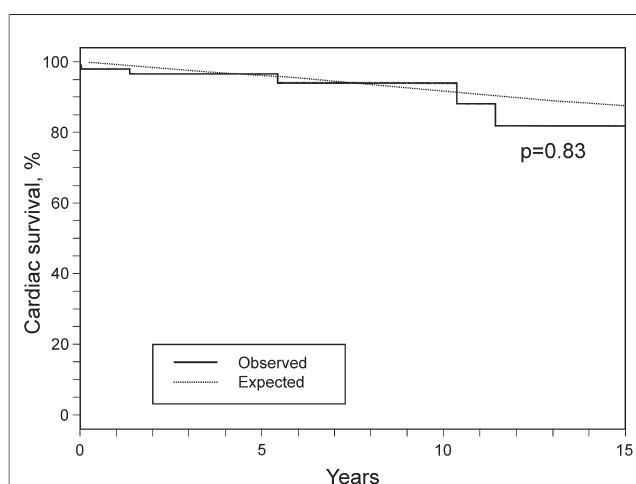


**Figure 2** Survival of Patients With ABS Versus an Age- and Gender-Matched Population

Kaplan-Meier curves showing estimated survival over time. Expected survival of an age- and gender-matched population (expected) is shown along with survival of patients with apical ballooning syndrome.

The recurrence of ABS is infrequent: an average yearly recurrence rate of 2.9% over the first few years after the first event, subsequently decreasing to 1.3% per year over the remainder of follow-up. The relatively small number of recurrences unfortunately precluded further analyses of predictors and outcomes. Although ABS is associated with a hyperadrenergic state (8), beta-blockade did not fully prevent recurrences.

We report 4-year morbidity associated with ABS. Almost one-third of the patients continued to have episodes of chest pain, and up to one-third of these patients required admis-



**Figure 3** Cardiovascular Survival of Patients With ABS Versus an Age- and Gender-Matched Population

Kaplan-Meier curves showing estimated cardiovascular survival over time. Expected cardiovascular survival of an age- and gender-matched population (expected) is shown along with cardiovascular survival of patients with apical ballooning syndrome.



sion for evaluation and management of chest pain (1). In those patients who had repeat coronary angiography, the study showed no progression of atherosclerosis, highlighting the difference in the pathophysiology between chest pain in patients with ABS and patients with typical angina secondary to atherosclerotic heart disease.

Previous reports have commented only on the short-term survival of patients with ABS (3,5,6). In our study, patients with ABS had similar 4-year survival and cardiovascular survival to an age- and gender-matched population. The 4-year prognosis of patients with ABS remains excellent, paralleling the general clinical course of quick symptom resolution.

In our case series, we observed no prognostic value of troponin or B-type natriuretic peptide levels, and the ECG findings at index hospitalization did not predict short-term or long-term survival. These features continue to distinguish ABS from acute coronary syndromes.

**Study limitations.** The present study consists of a relatively small cohort of retrospectively identified patients with a rare condition that mimics acute coronary syndrome. Limitations in our analysis include the small number of hard end points, which limits the analysis and the conclusions that can be drawn from this analysis. Treatment of the patients was empirical and may reflect treatment biases for which we cannot account or adjust fully. Other limitations include the lack of systematic measurements of neurohormones and cardiac enzymes; the maximal troponin T value was available in only 47 patients beginning in 2001, although all patients had at least 1 cardiac enzyme set available.

## Conclusions

Data from our case series of ABS cases suggest that recurrence is infrequent. The 4-year prognosis of patients with ABS was similar to that expected in an age- and gender-matched population.

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